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ABPA and Fungal Sensitization in Upper and Lower Respiratory Disease; Focus on Allergic Fungal Sinusitis

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Disclosure

- No relevant financial relationships to disclose

Learning Objectives

Upon completion of this session, participants should be able to:

- Describe the role of fungi in inducing intense allergic inflammation in allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis
- Describe the controversial role of fungi in inducing eosinophilic inflammation in chronic rhinosinusitis

Invasive Fungal Rhinosinusitis

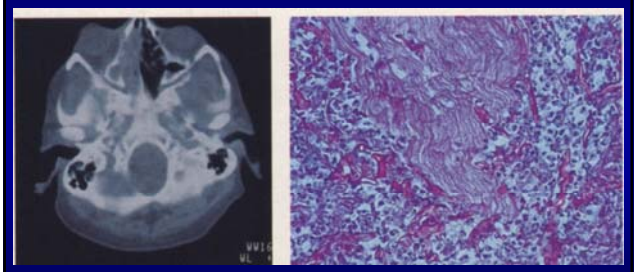
- Acute fulminate necrotizing fungal rhinosinusitis
- Chronic invasive fungal rhinosinusitis
- Granulomatous invasive fungal rhinosinusitis

Noninvasive Fungal Rhinosinusitis

- Fungal ball (sinus mycetoma)
- Allergic fungal rhinosinusitis (AFS)
  - 6-9% of all chronic rhinosinusitis (CRS)

From: deShazo RD, Chapin K, Swain RE. *N Engl J Med* 1997;337:254-9.
Schubert MS. *Otolaryngol Clin North Am* 2004;37:301-326.

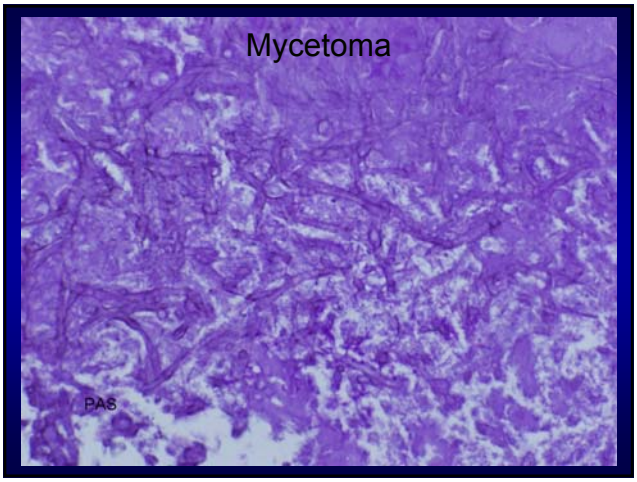
Acute Fulminate Necrotizing Fungal Rhinosinusitis ("Mucormycosis")



58 y.o. renal transplant (culture result not reported).

From: Andrews PA. *Lancet* 2001;357:2001.

Mycetoma



Allergic Fungal Sinusitis
Clinical/Surgical Presentation

- Chronic rhinosinusitis (CRS) with nasal polyps (also called hypertrophic/hyperplastic sinus disease (HSD), chronic eosinophilic rhinosinusitis, etc).
- Characteristic "allergic mucin" is seen grossly at surgery and further defined histopathologically.

Allergic Fungal Sinusitis (2)
Clinical/Surgical Presentation (cont.)

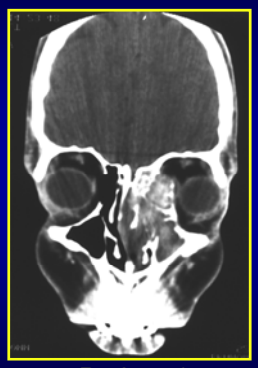
- Allergic mucin is fungal stain positive for sparse scattered hyphae; non-tissue-invasive.
- Surgical sinus fungal culture usually positive (culture negative- 13%).

Allergic Fungal Sinusitis (3)

Clinical/Surgical Presentation (cont.)

- Sinus CT hyperattenuation.
- Can be bi- or unilateral.
- Fungal-containing allergic mucin can erode through sinus bone margins into orbit or intracranium.
- Clinically chronic and often surgically recurrent.

Allergic Fungal Sinusitis



Patient 1

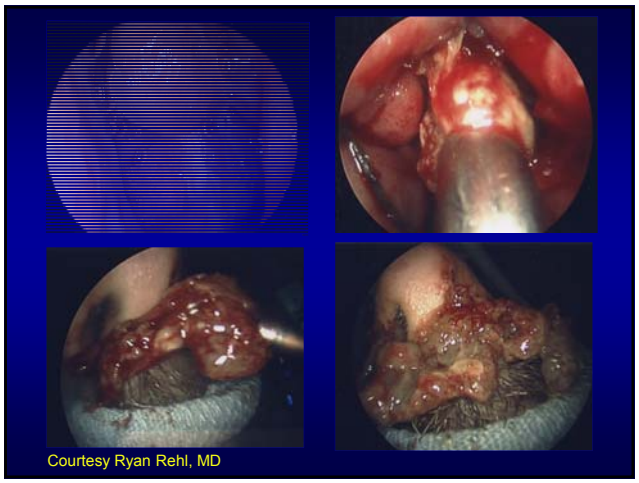
Patient 2

Allergic Mucin

Courtesy David Hecht, MD

Allergic Mucin

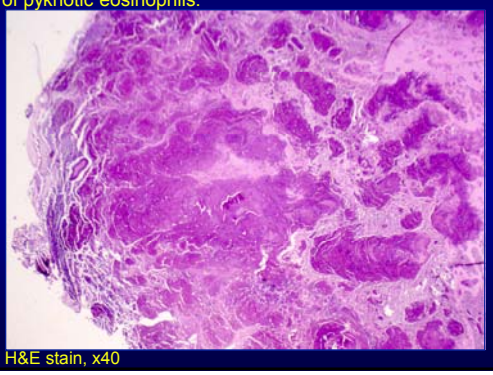
Courtesy David Hecht, MD



Courtesy Ryan Rehl, MD

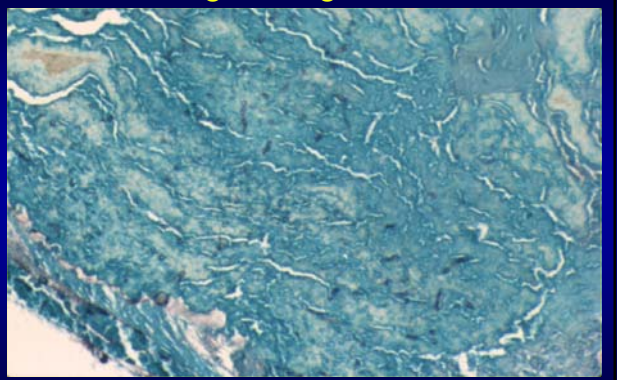
Allergic Mucin

- A histopathological, not functional, term.
- A sinus luminal viscoelastic inspissate of massive numbers of pyknotic eosinophils.



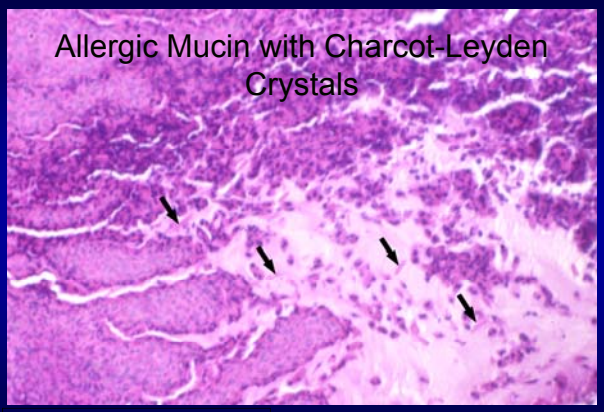
H&E stain, x40

Allergic Fungal Sinusitis



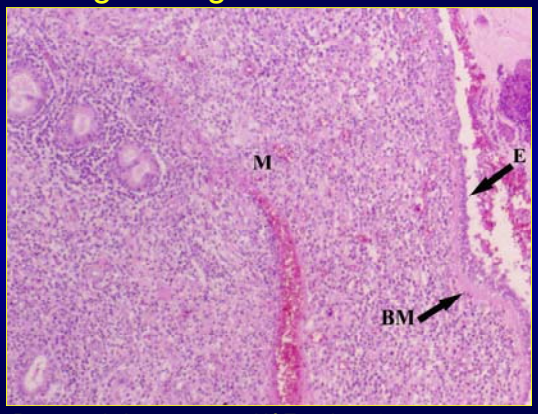
Paranasal sinus, allergic mucin- GMS stain, x100

Allergic Mucin with Charcot-Leyden Crystals



Surgical sinus H&E stain

Allergic Fungal Sinusitis Mucosa



Paranasal sinus mucosa. H&E stain x40

Minimum Required AFS Diagnostic Criteria (developed over 8 years and 67 consecutive AFS patients)

1) Characteristic "allergic mucin" must be seen: on surgical sinus histopathology or grossly at surgery.
2) Evidence for fungi: GMS (or similar) fungal stain must be positive for hyphae within the allergic mucin or surgical sinus fungal culture positive.
3) Characteristic sinus mucosal inflammatory infiltrate: small lymphocytes, plasma cells, eosinophils; no necrosis, granulomas, or fungal invasion.
4) Other fungal diseases are excluded.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

Allergic Fungal Sinusitis Pathophysiologic Findings

- Allergic/hypersensitivity response to the presence of fungi within the sinus cavity(s).
- All pts. are atopic- will be allergy skin test positive to multiple aeroallergens.
- All pts. will have specific IgE to the AFS etiologic fungus when properly identified by intraoperative surgical culture of allergic mucin.

- Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.
- Schubert MS. *Otolaryngol Clin North Am* 2004;37:301-326.
- Schubert MS. *Medical Mycology* 2009;47(Suppl 1):s324-s330.

Allergic Fungal Sinusitis Pathophysiologic Findings (cont.) (2)

- Incidence- 6-9% of all surgical sinusitis.
- Southern and Southwestern U.S. are endemic, but has been reported throughout the country and world.
- Chronic and often recurrent.

- Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.
- Schubert MS. *Otolaryngol Clin North Am* 2004;37:301-326.
- Schubert MS. *Medical Mycology* 2009;47(Suppl 1):s324-s330.

Allergic Fungal Sinusitis Pathophysiologic Findings (cont.) (3)

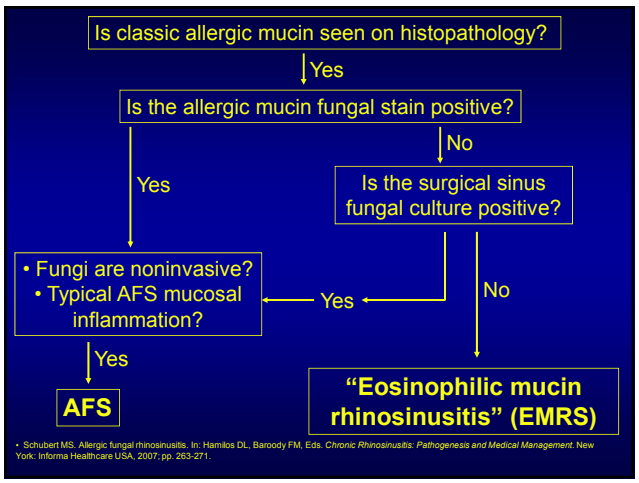
- Adults and children (mean age 33 y.o., range 8 y.o.- 67 y.o.).
- Nasal casts- 75%.
- Asthma- 64%.
- Immunocompetent.

- Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

Allergic Fungal Sinusitis Pathophysiologic Findings (cont.) (4)

- Associates with HLA-DQB1*0301 and *0302 (other CRS HLA-DQB1*0301, *0302, *0303, *0304, *0305).
- Analogous (but not identical) to allergic bronchopulmonary aspergillosis (ABPA).
- Most common causes:
  - "dematiaceous" fungi, e.g., *Bipolaris spicifera, Curvularia lunata, Exserohilum rostratum, Alternaria spp.*
  - *Aspergillus spp.*

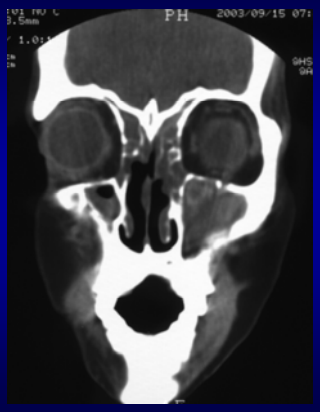
From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394 and Schubert MS, et al. *J Allergy Clin Immunol* 2004;114:1376-83.

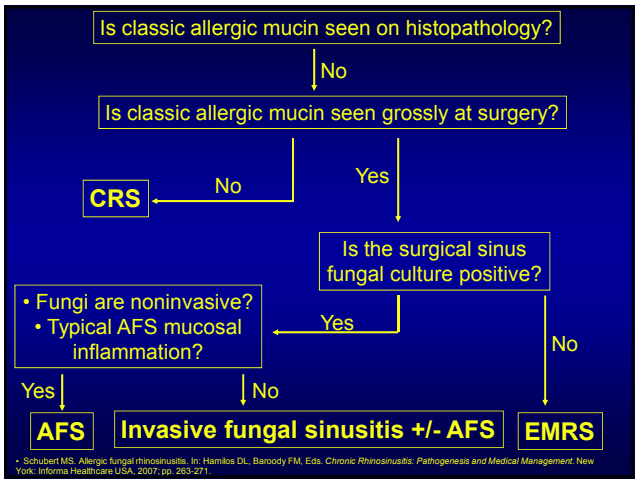


- Schubert MS. Allergic fungal rhinosinusitis. In: Hamilos DL, Baroody FM, Eds. *Chronic Rhinosinusitis: Pathogenesis and Medical Management.* New York: Informa Healthcare USA, 2007; pp. 263-271.

Eosinophilic mucin rhinosinusitis (EMRS)

36 y.o. female- CRS with nasal polyps, classic inspissated allergic mucin (EMRS), asthma, and inhalant atopy. Not ASA/NSAID sensitive. Negative for fungi on cultures and histopathology from all sinus surgeries.





ABPA and AFS Compared

	ABPA	AFS
• allergic mucin with noninvasive fungal hyphae	yes	yes
• respiratory atopy	yes	yes
• allergy skin test positive to fungal organism	yes	yes
• total serum IgE elevated	yes	yes
• fungal-specific IgG elevated	yes	yes
• fungal-specific IgE elevated beyond common atopy	yes	no
• serum precipitins to fungal organism	yes	no
• peripheral eosinophilia	yes	no/yes
• change in total serum IgE prognostic	yes	yes

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

(2)

ABPA and AFS Compared (cont.)

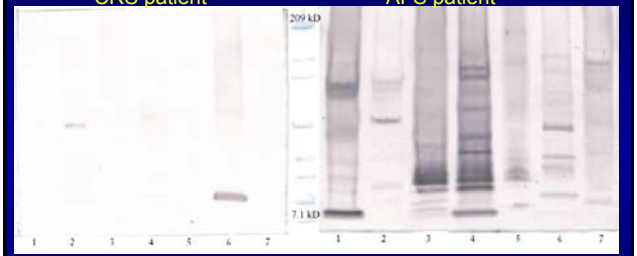
	ABPA	AFS
• MHC class II association	yes[a]	yes[b]
• Favorable clinical response to systemic corticosteroids	yes	yes[c]

[a] HLA-DR2 and DR5; DQ2 was found to be protective. From: Chauhan B, Santiago L, Hutcheson PS, et al. *J Allergy Clin Immunol* 2000;106:723-9.

[b] HLA-DQB1*0301 and *0302 for *B. spicifera* AFS. From: Schubert MS, Hutcheson PS, Graff RJ, et al. *J Allergy Clin Immunol* 2004;114:1376-83.

[c] From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:395-402.

Figure 1. Representative IgE anti-fungal immunoblots from a CRS patient and an AFRS patient.



From: Hutcheson P, Schubert MS, Slavin RG. *Am J Rhinol Allergy* 2010:24;405-8.

Table 4. Comparison of mean number of positive IgE bands for each fungu s between 10 AFRS and 11 CRS subjects.

Fungus	AFRS mean (SD)	CRS mean (SD)	Significance[1] *p*
Alternaria	6.9 (1.8)	0.6 (0.9)	<.001
Aspergillus	5.2 (4.1)	0.7 (0.9)	<.01
Bipolaris	8.4 (1.9)	0.8 (1.8)	<.001
Bipolaris/Curvularia	10.7 (1.5)	1.6 (1.8)	<.001
Epicoccum	6.7 (3.1)	0.8 (2.4)	<.001
Fusarium	4.1 (2.1)	0.7 (0.6)	<.01
Phoma	4.9 (2.5)	0.9 (2.2)	<.01

[1]Independent-samples t test

From: Hutcheson P, Schubert MS, Slavin RG. *Am J Rhinol Allergy* 2010:24;405-8.

Data to Support Fungal Pathogenesis of Common CRS

- Intraoperative fungal cultures 56% positive in 45 random CRS patients.[1]
- Mucus from surgical specimens in 54 CRS patients 100% positive for chitin (polymer of *N*-acetylglucosamine) (Dr. Ponikau).[2]
- Middle meatus BX- PCR using common fungal primer 6.5% positive in CRS and 0% positive in controls; if CRS has polyps, atopy, and asthma- 29% positive.[3]
- PBMCs from 18 CRS patients produce IL-5 when stimulated with Alternaria (but not Aspergillus, Cladosporium, or Penicillium) *in vitro* (Dr. Ponikau).[4]

1. Lebowitz RA e. al. *Laryngoscope* 2002;112:2189-2191.
2. Taylor MJ et al. *Otolaryngol Head Neck Surg* 2002:127:377-383.
3. Rao AK et al. *Otolaryngol Head Neck Surg* 2006;134:581-585.
4. Shin SH et al. *J Allergy Clin Immunol* 2004;114:1369-1375.

Data to Support Fungal Pathogenesis of Common CRS (cont.) (2)

- Double-blinded 6 mos. of topical sinonasal amphotericin B (10 patients) improved CRS mucosal thickening by 8.8%; placebo (14 patients) worsened by 2.5% (Dr. Ponikau).[5]
- Ricchetti et al.[6] Four weeks, 74 pts.- CRS with polyps- 20 ml of 100 ug/ml ampho B. intranasal twice daily- complete resolution of nasal polyposis in 29 pts. (39%). Unblinded uncontrolled study.

5. Ponikau JU et al. *J Allergy Clin Immunol* 2005;115:125-131.
6. Ricchetti A et al. *J Laryngol Otol* 2002;116:261-263.

Data Against Fungal Pathogenesis of Common CRS

- 788 surgical pathology specimens from 384 consecutive cases from Dept. of Pathology/Baylor- 47 cases (12%) had some type of fungal sinusitis: 34 had AFS, 11 had fungal ball/mycetoma, 1 had chronic invasive, and 1 had acute fulminate fungal sinusitis.[1]
- PCR for fungal DNA- nasal specimens- 42% positive in 25 CRS pts., 40% positive in 18 controls.[2]
- PCR for fungal DNA- sinus mucosa- 6.5% positive in 31 CRS pts., 0% positive in 14 controls.[3]

1. Granville L et al. *Hum Pathol* 2004;35:474-481.
2. Catten MD et al. *Laryngoscope*;2001;111:399-403.
3. Rao AK et al. *Otolaryngol Head Neck Surg* 2006;134:581-585.

Data Against Fungal Pathogenesis of Common CRS (cont.) (2)

- Nasal endoscopy- fungal culture of paranasal sinus secretions in 50 CRS and 24 control pts.- positive in 2 CRS pts., negative in all controls.[4]
- Neither Alternaria nor Aspergillus were able to stimulate IL-5 or γ-interferon transcription *in vitro* from PBMCs from 14 CRS pts. and 7 controls.[5]
- Other double-blind placebo controlled studies- topical and systemic antifungal treatments found ineffective in CRS treatment.[6-11]

4. Bhattacharyya N. *Laryngoscope* 2007;117:2041-2044.
5. Douglas R et al. *Laryngoscope* 2007;117:411-414.
6. Weschta M et al. *J Allergy Clin Immunol* 2004;113:1122-8.
7. Shin SH, Yee MK. *Acta Otolaryngol* 2004;124:1174-1177.
8. Kennedy DW et al. *Laryngoscope* 2005;115:1793-9.
9. Ebbens FA et al. *J Allergy Clin Immunol* 2006;118:1149-56.
10. Weschta M et al. *Arch OtolaryngolHead Neck Surg* 2006;132:743-747.
11. Liang KL et al. *Am J Rhinol* 2008;22:52-58.

Allergic Fungal Sinusitis Treatment

- Aggressive sinus surgery.
- Topical corticosteroids.
- Antihistamines.
- Consider antileukotrienes.

- Schubert MS. Allergic fungal rhinosinusitis. In: Hamilos DL, Baroody FM, Eds. *Chronic Rhinosinusitis: Pathogenesis and Medical Management.* New York: Informa Healthcare USA, 2007; pp. 263-271.
- Schubert MS. *Med Mycology* 2009;47(Suppl 1):s324-s330.

Allergic Fungal Sinusitis Treatment (cont.) (2)

- Allergen immunotherapy (etiologic mold may be included).
- Oral corticosteroids (OCS)- modified ABPA OCS or similar protocol (pre-op, intra-op, or ASAP post-op).
- Close medical-surgical cooperation and F/U.
- Monitor total serum IgE post-op.

- Schubert MS. Allergic fungal rhinosinusitis. In: Hamilos DL, Baroody FM, Eds. *Chronic Rhinosinusitis: Pathogenesis and Medical Management.* New York: Informa Healthcare USA, 2007; pp. 263-271.

Allergic Fungal Sinusitis Treatment (cont.) (3)

- Systemic antifungals (oral, parenteral) - not felt to be effective.
- Topical antifungals - not adequately studied yet; does make sense. Maybe as adjunct to OCS (eg., OCS + itraconazole in ABPA)?
- Omalizumab (anti-IgE)???

- Schubert MS. Allergic fungal rhinosinusitis. In: Hamilos DL, Baroody FM, Eds. *Chronic Rhinosinusitis: Pathogenesis and Medical Management.* New York: Informa Healthcare USA, 2007; pp. 263-271.
- Schubert MS. *Medical Mycology* 2009;47(Suppl 1):s324-s330.

AFS oral corticosteroid (OCS) protocol (1)

- Start post-operatively ASAP:
  - 0.5 mg prednisone/kg q AM for 2 weeks, then 0.5 mg/kg every other AM for 2 weeks with gradual taper to 7.5-5 mg prednisone every other AM by 3 months and continue on this dose.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

AFS OCS protocol (cont.) (2)

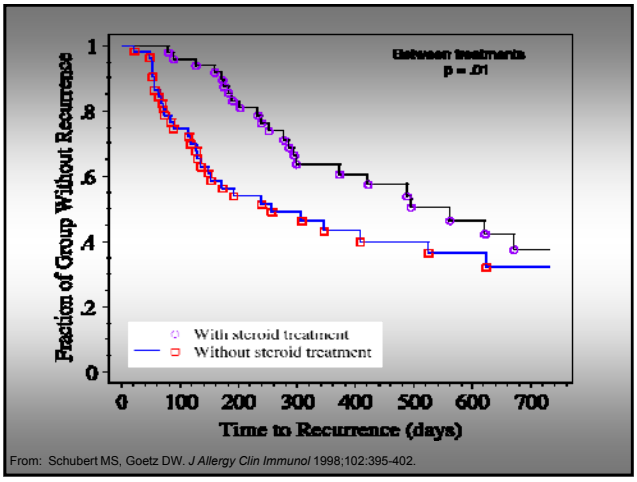
- Short "burst" of prednisone for any intercurrent acute rhinosinusitis episodes (with or without antibiotics as indicated).
- Discontinue prednisone at 1 year, sooner, or later, as indicated.
- If AFS surgically recurrent- restart OCS from time "zero" and repeat.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

Allergic Fungal Sinusitis
Treatment Conclusions

- OCS significantly reduced rhinosinusitis symptoms and helped to forestall the need for recurrent sinus surgery.
- No significant side effects were seen with this AFS OCS protocol.
- Changes in both total serum IgE and fungal-specific IgG levels correlated with clinical status.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.



From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:395-402.

Rupa V, Jacob M, Mathews MS, Seshadri MS. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. *Eur Arch Otorhinolaryngol* 2010;267:233-238.

Design:
- 24 AFS pts.- randomized to receive OCS (n=12) or placebo (n=12) in the immediate postoperative period.
- OCS- 50 mg prednisolone daily for 6 weeks, then gradual taper off over 6 more weeks.
- All patients received nasal steroid spray and oral itraconazole (200 mg daily)

Results:
- OCS- 8 of 12 pts. disease-free at 6 weeks; 12 of 12 pts. disease-free at 12 weeks.
- Placebo- 1 of 12 pts. disease-free at 6 weeks; 1 of 12 pts. disease-free at 12 weeks.

Conclusions:
- OCS postoperatively are beneficial in AFS.
- Oral itraconazole ineffective in AFS.
- Need for addition of oral itraconazole to OCS was unaddressed.

AFS Pre-RX

- 17 y.o. male.
- 3 prior surgeries.
- *Bipolaris spicifera* cultured from previous surgeries.
- Failed 6 mos. oral itraconazole.

AFS Post-RX (3 year F/U)

- Underwent surgery #4.
- Given AFS OCS protocol for 1 yr.
- Topical steroids, antihistamines.
- Allergen I.T. to all relevant aeroallergens.